The etiology and response to high dose oral prednisone in children with infantile spasms - a resource-poor country perspective

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Declaration

By submitting this thesis electronically, I declare that the entirety of the work contained therein is my own original work, that I am the authorship owner thereof (unless to the extent explicitly otherwise stated) and that I have not previously in its entirety or in part submitted it for obtaining any qualification.

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Date: December 2019

Abstract

Background and objective: Hormonal therapy is the treatment of choice in most infants with infantile spasms (IS). Intramuscular adrenocorticotropic hormone (ACTH) has historically been the treatment of choice, however, its usage is complicated by unavailability and financial constraints, even more so in resource limited settings. Our institution has used high dose prednisone as the first-line hormonal treatment of infantile spasms since 2006. In this study we investigated the efficacy and safety of high dose oral prednisone. In addition, we describe the most common causes of IS in our setting.

Methods: Medical records of infants who presented to Tygerberg Hospital with IS and who were treated with high-dose oral prednisone (4mg/kg/day), from September 2012 through August 2016, were reviewed. Electro-clinical response was defined as clinical spasm-freedom and resolution of hypsarrythmia within two weeks of initiation of therapy.

Results: Over the 4-year period, 50 children with new-onset IS were treated. The mean duration of epileptic spasms prior to initiation of treatment was 15.4 days (range 7.64-23.176 days) and the mean age of diagnosis was 22.83 weeks (range 19.19-26.47 weeks). The majority of infants (78%) exhibited developmental delay prior to the onset of spasms. Hypoxic ischemic encephalopathy and white matter injury of prematurity, were the most common etiologies. Electro-clinical response occurred in 32 (64%) of infants within two weeks of the onset of treatment. No major side effects were encountered during the treatment period.

Conclusion: Our results continue to demonstrate that high dose oral prednisone is very effective for the treatment of new-onset infantile spasms, with no major adverse effects. Oral prednisone represents a less expensive, readily available alternative to ACTH injections, especially in resource-constrained settings. A significant proportion of IS cases can be attributed to potentially preventable etiologies such as hypoxic ischemic encephalopathy, white matter injury of prematurity and hypoglycemic encephalopathy.

Opsomming

Agtergrond: Hormonale terapie is die behandeling van keuse vir die meeste kinders met infantiele spasmas (IS). Intramuskulêre adrenokortikotrofiese hormoon (AKTH) is histories die behandeling van keuse, maar die gebruik daarvan word gekompliseer deur ontoereikenheid and finsiële beperkings veral in beperkte hulpbronne instansies. Hoë dosis prednisoon word as eerste linie hormonale terapie vir IS by Tygerberg Hospitaal gebruik. In hierdie studie word die effektiwiteit en veiligheid van hoë dosis prednisoon ondersoek. Verder, word ook die mees algemene oorsake van IS, by ons instansie, beskryf.

Metodes: Die mediese rekords van kinders wat by Tygerberg Hospitaal presenteer het met IS en met hoë dosis orale prednisoon (4mg/kg/dag), vanaf September 2012 tot en met Augustus 2016 behandel is, was na gegaan. Elektro-kliniese respons was gedefinieer as klinies spasma vryheid en resolusie van hipsaritmië binne twee weke vanaf die begin van behandeling.

Resultate: ‘n Totaal van 50 kinders, oor ‘n 4 jaar periode, was met nuwe aankoms IS by Tygerberg Hospitaal behandel. Die gemiddelde duur van spasmas voor die begin van behandeling was 15.4 dae (omvang 7.64-23.176 dae) en die gemiddelde ouderdom met diagnose was 22.83 weke (omvang 19.19-26.47 weke). Die meerderheid van kinders (78%) het ontwikkelingsagterstand getoon voor die begin van spasmas. Hipoksiese isgemiese enkefelopatie en witstof besering van premaruteit was die mees algemeenste oorsake. Elektro-kliniese respons was behaal in 32 (64%) van kinders binne twee weke van die aanvang van behandeling. Geen nadelige effekte was aangemeld tydens die behandelingsperiode.

Gevolgtrekking: Die resultate demonstreer dat hoë dosis prednisoon ‘n baie effektiewe behandeling vir nuwe aankoms IS is, met geen noemenswaardige nadelige effekte nie. Orale prednisoon is ‘n meer bekostigbare, maklik verkrygbare alternatief tot AKTH intramuskulêre inspuitings, veral by ‘n beperkte-hulpbron instelling. ‘n Groot hoeveelheid van IS gevalle het potensieël ‘n voorkombare etiologie, soos hipoksiese isgemiese enkefelopatie, witstof besering van premaruteit and hipoglusemiese enkefelopatie.

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A special thank you to my husband and daughter for all the sacrifices you had to make and for your endless love and belief in me.

Dedications

I dedicate this work to my daughter, Lira. You are my passion and proof that dreams do come true. I love you always.

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List of Abbreviations

IS: Infantile spams
ACTH: Adrenocorticotropic hormone
EDL: essential drug list
EEG: electroencephalogram
MRI: Magnetic resonance imaging
HIE: Hypoxic ischemic encephalopathy
PVL: Periventricular leukomalacia
TSC: Tuberous sclerosis complex
ILAE: International League against Epilepsy
UKISS: United Kingdom Infantile Spasms Study
TCH: Tygerberg Children's Hospital
XLAG: X-linked lissencephaly with abnormal genitalia
TBH: Tygerberg Hospital
ECM: Enterprise Content Management
CRF: case report form
PEHO: Progressive encephalopathy with edema, hypsarrhythmia and optic atrophy

Chapter 1: Introduction

1.1 Background

Infantile spasms (IS) are a rare seizure disorder that primarily occurs during the first year of life, especially between the third and eighth months. The syndrome of IS consists of a constellation of myoclonic-like seizures, whose electroencephalogram (EEG) pattern is that of hypsarrhythmia, a disorganized high-voltage pattern with no normal background. The triad of spasms, developmental arrest or regression and hypsarrhythmia is known as West Syndrome.

1.2 Problem Statement

The etiology of IS is highly varied and includes perinatal brain injuries, postnatal infections, neurocutaneous syndromes, cerebral malformations and trauma. Few studies have investigated the causes of IS in infants residing in resource poor countries. We postulate that the greatest proportion of cases in our setting will be due to perinatal factors [hypoxic ischemic encephalopathy (HIE) and white matter injury of prematurity].

Management of infants with IS in resource-limited settings is constrained by delay in diagnosis and potentially the high cost of treatment. The optimal treatment of IS is unclear but many studies advocate hormonal treatment (prednisolone or ACTH). A 2008 Cochrane review suggested that hormonal treatment was better that Vigabatrine. Vigabatrin and ACTH are expensive and not readily available in many parts of South Africa. Oral corticosteroids are a logical, less expensive alternative and the efficacy of high dose prednisolone 4mg/kg/day is supported by the findings of the United Kingdom Infantile Spasms Study (UKISS). Prednisone is on the essential drug list (EDL) for South African public hospitals and therefore readily available at all health care levels. The aim of the study was to investigate the efficacy and safety of high dose (4 mg/kg/day) prednisone in a consecutive cohort of infants with IS residing in the Western Cape province of South Africa. We postulate that the efficacy of oral prednisone would be equivalent to published efficacy rates for prednisolone.

Chapter 2: Literature Review

2.1 Introduction

Infantile spasms occurs in all ethnic groups. Some studies have found that boys and girls are affected equally, while others suggest that boys are somewhat more likely to be affected.[1] A positive family history of IS occurs in 1-7% of cases, suggesting a genetic susceptibility. The evaluation of an infant with suspected IS should include an EEG and a search for treatable disorders and precipitating factors. Magnetic resonance imaging (MRI) is the special investigation modality with the highest diagnostic yield as it may identify etiological causes such as cortical malformations, hypoxic ischemic encephalopathy (HIE), periventricular leukomalacia (PVL), intra-uterine infections and tuberous sclerosis complex (TSC).

2.2 Classification

Previously, the International League against Epilepsy (ILAE) classified IS according to the underlying etiology as follows:

1. **Idiopathic**: Patients with normal development at onset, normal examination and neuroimaging, and hypsarrhythmia EEG pattern without focal epileptiform abnormalities.
2. **Symptomatic**: evidence of pre-existing brain insults due to antenatal/perinatal or postnatal causes, including brain malformations, hypoxic ischemic encephalopathy (HIE), periventricular leukomalacia (PVL), infections, or inborn errors of metabolism.
3. **Cryptogenic**: Presumed underlying causes due to neurological or developmental abnormality, but investigations are inconclusive.

The ILAE revised classification and terminology of seizures and epilepsies, published in 2010, designated West syndrome as an electroclinical syndrome with onset in infancy and epileptic spasms as a type of seizure. It furthermore recommended that the causes of IS should instead be classified as:

1. **Genetic** (examples include trisomy 21, and ARX and CDKL5 mutations)
2. **Structural/Metabolic**
3. **Unknown** (no underlying cause identified).

2.3 Etiology

The proportion of etiological categories of IS varies among different studies. In a prospective, multicentre study on the evaluation of new-onset IS from the National Infantile Spasms Consortium, 251 infants were enrolled, and a cause was identified in 161 patients (64%).[2] The most commonly identified causes were structural acquired (22%), genetic (14%), structural congenital (11%), genetic structural (10%), metabolic (5%) and infection (2%). Clinical evaluation with MRI provided a specific diagnosis in 55% of the infants.

The critical time of the insult typically occurs in the prenatal, perinatal or postnatal period. Pre- or perinatal complications account for the greatest proportion of cases (45.6%).[2] Down syndrome was the most common genetic cause (42% of purely genetic etiologies). Tuberous sclerosis accounted for nearly half of genetic-structural etiologies.[2] About 10% of those with IS have TSC and roughly half of those with TSC develop IS.[3]

2.4 Treatment

Infantile spasms are notoriously difficult to treat, as it often is unresponsive to conventional anti-epileptics. Most specialist centers advocate hormonal treatment (adrenocorticotrophic hormone (ACTH) and prednisolone). The 2004 United Kingdom Infantile Spasms Study (UKISS)[4] assessed the relative efficacy of hormonal treatment (prednisolone or ACTH) and vigabatrin in a multi-centre, randomized-controlled trail in 150 hospitals in the UK. The primary study outcome was cessation of spasms within 2 weeks. Minimum doses were vigabatrin 100mg/kg per day, oral prednisolone 4 mg/kg per day, or intramuscular tetracosactide depot 0.5mg (40 IU) on alternative days. Analysis was by intention to treat. Hormonal therapy was successful in 73% of infants after 2 weeks compared with vigabatrin in 54%. Adverse effects were reported in 55% of infants on hormonal treatment and 54% of infants on vigabatrin (i.e. no statistical difference) No deaths were recorded. This study and a subsequent Cochrane review recommended that hormonal therapy was more effective than vigabatrin in the short term.[5]

Two earlier studies comparing oral 2mg/kg/day prednisone and intramuscular 150U/m^2/day ACTH reported that oral corticosteroids were less effective.[6,7] However, in the UKISS, a higher dose 4-6 mg/kg/day oral prednisolone was found to be equivalent to synthetic ACTH (70% vs. 76% spasm freedom after 14 days, respectively).[4] The effectiveness of a higher dose of prednisolone was also illustrated in subsequent studies[8,9] and oral prednisolone had fewer adverse effects and was less expensive than ACTH.[9] Hussain et al showed that 63% of patients responded completely to prednisolone 8mg/kg/day[8]. The underlying cause seems to influence choice of treatment as well, since Vigabatrin has proven to be particularly effective where the underlying diagnosis were TSC.[10]

In resource-constrained settings, availability and affordability of drugs are of critical importance. ACTH is expensive [R 345.01 per vial (1mg/1ml)], not freely available, not without adverse effects and has to be administered by intramuscular route. In contrast, prednisone (R 14.96 per 100, 5 mg tablets) is less expensive, easily available (on the EDL) and can be given orally.

Raga SV et al. conducted a systemic review of the literature to access the quality of evidence of prednisone and prednisolone for the management of epileptic spasms.[11] The study concluded that there is class III evidence (level C recommendation) to support the efficacy of oral prednisone compared to class IV evidence for ACTH. Accordingly, they then proposed a treatment algorithm based on the availability of vigabatrin and ACTH. Prednisone 4mg/kg/day was recommended in settings were either vigabatrin was available but ACTH not available or both ACTH and vigabatrin were unavailable. Additional randomized-controlled trials (RCT) were recommended to compare oral corticosteroids to ACTH and to determine the optimal dose, comparison efficacy, as well as long-term studies looking at the neurodevelopmental outcomes of these groups.

More recently, the results of a multicentre open-label randomized trial was published which explored whether combined therapy would be more effective than hormonal therapy in isolation.[12] The authors found hormonal therapy with vigabatrin significantly more effective at stopping IS than hormonal therapy alone. However, combination therapy did not result in improved development or epilepsy at 18-months follow-up.

Chapter 3: Method

3.1 Aim and objectives

The aim of the study was to determine the efficacy and safety of high dose oral prednisone 4mg/kg/day in the treatment of infants with IS.

Secondary objectives were**:**

1. To describe the etiology of infantile spasms
2. To determine whether the underlying etiology influences response to therapy
3. To describe whether the baseline EEG background pattern influences response to therapy
4. To describe the yield of special investigations (MRI) in children with IS

3.2 Research design

This was a retrospective analysis of all children presenting with infantile spasms to the paediatric neurology service at Tygerberg Hospital (TH) over a four-year period (September 2012 till August 2016.)

3.3 Study site

The paediatric wards are situated in the G-Block of Tygerberg Hospital, the academic training hospital of the Stellenbosch University. This hospital's paediatric wards serves the immediate surrounding areas, providing primary and secondary health care to children, as well as tertiary care to all paediatric patients in Metro East district of Cape Town, as well as the northern and eastern rural districts of the Western Cape. Paediatric patients with epilepsy are diagnosed and managed in ward G9, a tertiary paediatric neurology ward. Epilepsy is one of the most common presenting complaints in children referred to the ward.

3.4 Study Population and Sampling

The target population was all children with suspected IS referred to the tertiary paediatric neurology service at TH. All subjects underwent baseline EEG recording to ascertain the presence of hypsarrhythmia or its variants.

Inclusion criteria: All infants between the ages of 3 months and 1 year with IS were included.
Exclusion criteria: Inadequate clinical information.

Study participants were systematically identified from the neurological ward and EEG database at TH.

3.5 Operational definitions

For the purpose of the study, the following definitions was used:

- Sex: Male or Female
- Low birth weight was defined as a birth weight less than 2,5 kg
- Late preterm were defined as infants born between 34 weeks and 0 days and 36 weeks and 6 days gestational age. Term infants were born at a gestational age > 37 weeks
- A 5-minute Apgar score of 7-10 was considered as reassuring, a score of 4-6 as moderately abnormal and a score of 0-3 as low in the term and late-term infant
- Microcephaly was defined as a head circumference which is more than 2 standard deviations below mean for gestational age and gender. Marcocephaly was defined as a head circumference > 2SD above the mean for gestational age and gender.
- Neonatal seizures were defined as seizures within the first 28 days of life.
- Idiopathic IS refers to infants with normal development at onset, normal examination and neuroimaging, and hypsarrhythmia EEG pattern without focal epileptiform abnormalities.
- Symptomatic IS refers to infants with evidence of pre-existing brain insult due to antenatal/perinatal or postnatal causes, including brain malformations, hypoxic ischemic encephalopathy (HIE), periventricular leukomalacia (PVL), infections, or inborn errors of metabolism.
- Satisfactory response (treatment response): Complete cessation of spasms (both EEG and clinical responses) within 2 weeks of therapy.

3.6 TH IS investigation and treatment algorithm

Infants were evaluated by detailed history, physical examination and pertinent investigations were carried out. Patients were diagnosed with IS when they presented with characteristic epileptic spasms and supportive EEG background abnormalities (i.e. multi-focal discharges,

hyppsarrythmia or modified hyppsarrythmia). MRI/CT was performed in all children. Plasma amino acids, ammonia, lactate, pyruvate, urine organic acids, acid-base analysis and HIV-ELISA testing were performed where clinically indicated. Co-morbid conditions including visual and hearing problems were assessed and recorded. Tuberculin skin testing and chest radiography were requested in infants with tuberculosis risk factors. Molecular testing is locally available for mutations in the ARX gene. Indications for ARX mutation analysis include: X-linked lissencephaly with abnormal genitalia (XLAG), severe hydrocephalus, Proud syndrome (agenesis of the corpus callosum with abnormal genitalia), polymicrogyria with periventricular heterotopia and the clinical presence of dystonia. Early infantile epilepsy panel testing (invitae) was not available at the time of the study.

First-line therapy for all infants with IS consists of high dose (4 mg/kg/day) oral prednisone. A clinical response to treatment constituted a complete cessation of epileptic spasms and normalization of the EEG background within 2 weeks of therapy. For those children in whom the spasms were successfully treated, after 2 weeks of this dose, prednisone was then reduced gradually over a 2 week period. If spasms did not improve after 1 week, intramuscular ACTH (40 IU) was introduced. Vigabatrin was reserved for the treatment of TSC-associated IS. Prior to treatment, serum electrolytes, glucose and blood pressure were measured. The presence of complications such as gastrointestinal hemorrhage, herpes simplex virus reactivation, tuberculosis reactivation and hypertension were noted.
Seizure (spasm) frequency was monitored by the nursing staff and caregivers who maintained a daily seizure diary. Side effects such as hypertension, irritability and glycosuria were noted.

3.7 Data collection

Data was primarily sourced from the admission book and discharge-summaries in the G9 paediatric neurology ward. TH uses an Open Text Enterprise Content Management (ECM) system where routine health information is captured. Medical staff, employed by TH, has password-protected access to view patient folders electronically. Documents and clinical information were obtained from ECM as well as data reviewed on the EEG reporting database using the unique hospital number.

Each patient enrolled in the study was assigned a unique patient identifier number. A paper-based case report form (CRF) was used to collect the data from the radiology database and clinical records. This data was then entered into an electronic database. Patient names, hospital numbers and physical addresses were not entered in the electronic database.

The data collected on the proforma included gender, age of onset with IS, age at diagnosis and initiation of treatment, type of spasms (flexor, extensor or others), etiological factors (perinatal events, mode of delivery, gestational age, presence of a neonatal encephalopathy and seizures, developmental delay, other postnatal complications (hypoglycemia), neurocutaneous syndrome, MRI and EEG findings as well as type of treatment and response.

All EEG's were reported by 2 paediatric neurologists (RVT and RS). For the study, the EEG's were classified into 3 types: type 1) Multi (focal) epileptic discharges < 50% of the non-REM EEG recording time, type 2) Bihemispherical epileptic discharges > 50% of the non-REM recording time with abnormal background activity (modified hypsarrythmia) and type 3) 90-100% irregular bi-hemispheric sharp wave activities in the non-REM EEG (hypsarrythmia).

3.8 Data analysis

This was a retrospective study, therefore descriptive analysis was performed. Data was analyzed using SPSS version 25 (SPSS Inc, Chicago, IL, USA). Descriptive statistics were used to analyse demographic data and outcome. Numerical variables were summarized using means and standard deviations, if the data was normally distributed. Medians and interquartile range were used when the data distribution was skewed. Categorical variables were described using proportions.

3.9 Limitations

Data was retrospectively analysed which may have impacted on the quality of the collected data. Limited study numbers did not allow extensive correlation testing. Sophisticated genetic testing was not available and therefore the percentages of genetic cases were most likely underestimated. Neurodevelopmental outcome data was not available.

3.10 Ethics

A request for a waiver of individual informed consent was requested and obtained from the Health Research Ethics Committee (HREC) at Stellenbosch University, as this was a retrospective review of routinely-collected data with minimal risk. Consent from the CEO of Tygerberg Hospital, as the custodian of this data, was obtained.

Data was extracted from the ward admission registers, patient records and the EEG database. A risk to patients is thus a breach of confidentiality. To minimize this, several

steps were undertaken: 1) data entered in electronic databases was password protected b) data was only communicated in anonymous form from the clinicians via encrypted data transfer for analysis purposes c) hard copies of the data were stored in a safe in a locked room.

This study was approved by the HREC of Stellenbosch University (S15/05/118)

The study findings are of importance as it may inform physicians of the efficacy and safety of high dose oral prednisone for the treatment of infants with IS in resource-constrained settings.

Chapter 4: Results

A total of 74 patients with IS were registered during the study period and 50 (67%) fulfilled the eligibility criteria. The clinical profile of the study population is shown in table 1. Males were predominant 58% (n=29). The mean duration of epileptic spasms prior to initiation of treatments was 15.4 days (range 1-168 days) and the mean age of diagnosis was 22.83 weeks (range 4-64 weeks). The majority of infants (78%) exhibited developmental delay prior to the onset of spasms.

Table 2 illustrates the etiological categories and precise etiologies of the study population. Structural-acquired causes represented by far the largest etiological category followed by “unknown” and genetic structural. The low percentage of pure genetic causes can be attributed to limited genetic diagnostic testing available. Hypoxic-ischaemic encephalopathy (HIE) and white matter injury of prematurity represented the most common etiologies.The diagnostic profile of children with IS is shown in table 3. Hypsarrythmia (62%) was the most common EEG finding. MRI was performed in all infants; it was normal in 28% of cases. Potentially preventable causes such as HIE, PVL and hypoglycemic encephalopathy were common MRI findings. Cerebral malformations were identified in 5 (10%) of cases and included such disorders as absence of the corpus callosum (Aicardi syndrome), open-lip schizencephaly, semi-lobar holoproscencephaly, perisylvian polymicrogyria and lissencephaly with band heterotopia. Metabolic workup was carried out in 10 (20%) of the infants. No inborn error of metabolism was identified in any of the cases.

Table 4 illustrates the therapeutic responses in the infants with IS. The satisfactory response rate of high dose oral prednisone in all the study subjects was 64% (32 out of 50 infants); 60% of the idiopathic IS cases and 64% of symptomatic cases responded favorably. Insufficient study numbers did not allow analysis of response to high dose prednisone in the

different etiological categories. Of interest was that none of the IS infants with genetic structural brain anomalies demonstrated a satisfactory high dose prednisone treatment response.

None of the children developed hypertension that was severe enough to warrant cessation of therapy and addition of hypertensive therapy. No major adverse events such as gastrointestinal bleeding or herpes simplex/TB reactivation were noted.

Chapter 5: Discussion – conclusion and recommendations

This study highlights the clinical profile and response to oral prednisone in children with IS at a tertiary center in the Western Cape Province of South Africa. We observed a slight male predominance (58%) in keeping with the 6:4 male-female ratio reported in the literature.[13] Male predominance is not a consistent finding in the literature. In this study it may reflect the predominance of males in the referral population. Alternatively, it may be due to the increasing vulnerability of HIE or neonatal hypoglycemia in male infants.[14] None of the study infants were HIV-infected, which is in keeping with the absence of studies reporting HIV-infection as a risk factor for IS.

In children with IS, treatment delay (even by 1 week) has been associated with poor long-term developmental outcomes.[15] It is therefore concerning that the mean duration of epileptic spasms prior to initiation of treatments in our setting was 15.4 days (range 1-168 days). We postulate that the cause of the delays are multif-actorial and are likely related to misdiagnosis and diminished access to specialty care. The majority of infants (78%) exhibited developmental delay prior to the onset of spasms and a significant proportion of these cases could be attributed to potentially preventable etiologies such as HIE, white matter injury of prematurity and hypoglycemic encephalopathy. Improved obstetric and neonatal care could potentially lower the prevalence of IS in our setting.

MRI represents the diagnostic modality of choice in the investigation of infants with IS. In our study, an underlying cause was identified in 62% of cases after adequate history-taking and physical examination. A genetic etiology was only identified in 8% of cases. The low percentage of pure genetic causes can be attributed to limited genetic diagnostic testing available in our resource constrained setting. A study conducted by the National Infantile Spasms Consortium of the United States reported a diagnostic yield of 11% when microarray-based comparative genomic hybridisation (aCGH) was instituted and 31% when early infantile epilepsy gene panels were used.[16]

Metabolic workup was carried out in 10 (20%) of the infants. No inborn error of metabolism was identified in any of the cases. Metabolic etiologies have been reported to be rare. Conditions that warrant exclusion include Pyridoxine dependency, biotinidase deficiency, PEHO syndrome, mitochondrial disorders, molybdenum co-factor deficiency and non-ketotic hyperglycinaemia. The reported response rate of high dose oral prednisone in other reported observational studies vary from 60-80%.[8,17,18] In our study, the satisfactory overall response rate was 64% (32 out of 50 infants); 60% of the idiopathic IS cases and 64% of symptomatic cases responded favorably. Insufficient study numbers did not allow analysis of response to

high dose prednisone in the different etiological categories. Of interest was that none of the IS infants with genetic structural brain anomalies demonstrated a satisfactory high dose prednisone treatment response. This warrants further investigation. No major adverse events such as gastrointestinal bleeding or herpes simplex/TB reactivation were noted.

Our results continue to demonstrate that high dose oral prednisone is very effective for the treatment of new-onset infantile spasms, with no major adverse effects. Oral prednisone represents a less expensive, readily available alternative to ACTH injections, especially in resource-limited settings. Our recommendation would be to use 4mg/kg/day oral prednisone as first line treatment for IS, in a limited-resource setting, and intramuscular ACTH (40IU) should be introduced for those that do not respond after 1 week of treatment with oral prednisone. Vigabatrin should be reserved for the treatment of TSC-associated IS.

A significant proportion of IS cases can be attributed to potentially preventable etiologies such as HIE, white matter injury of prematurity and hypoglycemic encephalopathy. Optimal obstetric and neonatal care could potentially lower the incidence of IS dramatically, thereby reducing the high morbidity associated with IS. Further studies should be done to compare the clinical response, optimal dose and long-term neurodevelopmental outcomes to high dose oral prednisone vs ACTH in the treatment of IS. A double-blind randomized control trial with good control over documentation, in a relatively larger study population, is recommended.

Appendices

Table 1: Clinical profile of the infants with infantile spasms (N=50)

Variable	n/N (%)
Male gender	29/50 (58)
Birth weight	
Low birth weight (< 2.5 kg)	15/50 (30)
Normal birth weight	34/50 (68)
Gestational age	
Preterm	6/50 (12)
Late preterm (34 -36 weeks 5 days)	5/50 (10)
Term (> 37 weeks)	38/50 (76)
5-minute Apgar score	
Reassuring > 7	38/50 (76)
Moderately abnormal 4-6	6/50 (12)
Low 0-3	1/50 (2)
HIV status	
Negative	46/50 (92)
Infected	0
Exposed uninfected	3/50 (6)
Not determined	1/50 (2)
Birth head circumference	
Normocephalic	29/50 (56)
Microcephalic	7/50 (14)
Macrocephalic	2/50 (4)
Neonatal seizures present	16/50 (32)
Prior AED prior to onset of IS	20/50 (40)
Developmental delay prior to onset of spasms	39/50 (78)
	Mean (SD)
Duration of spasms prior to treatment (days)	15.40 (26.44)
Age at diagnosis of IS (weeks)	22.83 (12.39)

AED= anti-epileptic drugs, IS= infantile spasms, SD= standard deviation

Table 2: Etiological categories and specific etiologies of the infants with infantile spasms (N=50)

Etiological categories	n/N (%)
Genetic	4/50 (8)
Genetic structural	8/50 (16)
Structural congenital	3/50 (6)
Structural acquired	20/50 (40)
Unknown	15/50 (30)
Specific etiology	
Hypoxic ischemic encephalopathy	7/50 (14)
White matter injury of prematurity	6/50 (12)
Hypoglycemic encephalopathy	2/50(4)
Tuberous sclerosis	5/50 (10)
Congenital brain malformation	5/50 (10)
Perinatal stroke	1/50 (2)
Hemorrhage	2/50 (4)
Post-meningitic squelae	0
Inborn errors of metabolism	0
Neurofibromatosis	1/50 (2)
Undetermined	17/50 (34)

Table 3: Diagnostic profile of infants with infantile spasms (N=50)

Special investigations	n/N (%)
Electroencephalogram	
Type 1 EEG	14/50 (28)
Modified Hypsarrhythmia	5/50 (10)
Hypsarrythmia	31/50 (62)
Specific MRI findings	
Normal	14/50 (28)
Abnormal	31/50 (62)
Hypoxia ischemia	6/50 (12)
WM injury of prematurity (PVL, IVH)	5/50 (10)
Cortical tubers (TSC)	5/50 (10)
Hypoglycemia	2/50 (4)
Perinatal stroke	1/50 (2)
Migration abnormality	4/50 (8)
Semi-lobar holoprosencephaly	1/50 (2)
Cerebral hypomyelination	1/50 (2)
Metabolic work up	0

EEG= electroencephalogram, PVL= periventricular leukomalacia, IVH= intraventricular haemorrhage, TSC= tuberous sclerosis complex

Table 4: Therapeutic response in infants with infantile spasms (N=50)

Response to prednisone	genetic	genetic structural	structural congenital	Structural acquired	unknown
Satisfactory response	3	4	0	13	12
Unsatisfactory response	1	4	3	7	3

Response to prednisone	symptomatic	Idiopathic
Complete response	29	3
Unsatisfactory response	16	2

Case report form (CRF)

Personal identifier	
Date of birth	
Folder number	
Gender: Male Female	
Antenatal problems	
Maternal substance abuse	
Birth weight: VLBW LBW NBW	
Gestational age: preterm, late-preterm term	
Apgar scores at 1 and 5 minutes	
HIV status: infected/uninfected/exposed/unknown	
Head circumference at birth	
Postnatal complications: IVH, HIE (Neonatal encephalopathy severity: mild moderate severe) Hypoglycemia, sepsis, meningitis	
Neonatal seizures: Yes or No	
Seizures before onset of IS Yes or No	
Prior anti-epileptic Rx Yes or No	
Age of onset IS: weeks	
Duration from onset of spasms (as observed by caregiver) and diagnosis/treatment (days)	
Baseline EEG:	
Etiology: genetic or structural metabolic or unknown	
Genetic testing: chromosomes ARX mutation & others	
MRI findings: Specify findings	
Metabolic testing findings (normal/abnormal)	
1st line regimen Prednisone Dose prednisone mg/kg Responder Yes No	
2nd line regimen: Required IM ACTH Responder Yes No	
Adverse effects on treatment: Hypertension, hypernatremia, hypokalemia, weight gain, edema infection, others	
Spasms free after 2 weeks	
EEG normalization after treatment	

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